

Differences in symptoms and pre-hospital delay among acute myocardial infarction patients according to ST-segment elevation on electrocardiogram: an analysis of China Acute Myocardial Infarction (CAMI) registry

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Abstract

Background: Approximately 70% patients with acute myocardial infarction (AMI) presented without ST-segment elevation on electrocardiogram. Patients with non-ST segment elevation myocardial infarction (NSTEMI) often presented with atypical symptoms, which may be related to pre-hospital delay and increased risk of mortality. However, up to date few studies reported detailed symptomatology of NSTEMI, particularly among Asian patients. The objective of this study was to describe and compare symptoms and presenting characteristics of NSTEMI *vs.* STEMI patients.

Methods: We enrolled 21,994 patients diagnosed with AMI from China Acute Myocardial Infarction (CAMI) Registry between January 2013 and September 2014. Patients were divided into 2 groups according to ST-segment elevation: ST-segment elevation (STEMI) group and NSTEMI group. We extracted data on patients' characteristics and detailed symptomatology and compared these variables between two groups.

Results: Compared with patients with STEMI ($N=16,315$), those with NSTEMI ($N=5679$) were older, more often females and more often have comorbidities. Patients with NSTEMI were less likely to present with persistent chest pain (54.3% *vs.* 71.4%), diaphoresis (48.6% *vs.* 70.0%), radiation pain (26.4% *vs.* 33.8%), and more likely to have chest distress (42.4% *vs.* 38.3%) than STEMI patients (all $P < 0.0001$). Patients with NSTEMI were also had longer time to hospital. In multivariable analysis, NSTEMI was independent predictor of presentation without chest pain (odds ratio: 1.974, 95% confidence interval: 1.849–2.107).

Conclusions: Patients with NSTEMI were more likely to present with chest distress and pre-hospital patient delay compared with patients with STEMI. It is necessary for both clinicians and patients to learn more about atypical symptoms of NSTEMI in order to rapidly recognize myocardial infarction.

Trial Registration: www.clinicaltrials.gov (No. NCT01874691).

Keywords: Non-ST segment elevation myocardial infarction; Symptom assessment; Time to treatment

Introduction

Chest pain is predominant symptoms of acute myocardial infarction (AMI). However, approximately one-third of AMI patients presented to hospital without typical chest pain.^[1] Previous studies have reported atypical presentation was independently associated with higher in-hospital mortality risk.^[2-7] AMI is traditionally classified into ST-segment elevation myocardial infarction (STEMI) and non-ST segment elevation myocardial infarction (NSTEMI) based on ST-segment elevation on electrocardiogram, and approximately 70% patients with acute coronary syndrome presented without ST-elevation.^[8]

There is significant difference in pathological process between STEMI and NSTEMI, which may lead to difference in symptoms. However, few studies up to date have reported symptoms of patients with NSTEMI in details, especially among Asian patients. The objective of this study was to describe and compare symptoms and presenting characteristics of NSTEMI *vs.* STEMI patients.

Methods

Ethical approval

This project was approved by the institutional review board central committee at Fuwai Hospital, National

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Center for Cardiovascular Diseases, China. The study was in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the *Declaration of Helsinki* 1975, as revised in 2000. Written informed consent was obtained from eligible patients before registration.

Study population

All patients included in this study were from China Acute Myocardial Infarction (CAMI) Registry. Details on trial designs have been described previously.^[9] Briefly, CAMI registry was a prospective multi-center registry conducted in China. Eligible patients were diagnosed with AMI according to the third Universal Definition for Myocardial Infarction, in which AMI was classified into type 1, 2, 3, 4a, 4b, 5.^[1] CAMI registry included patients with type 1, 2, 3 and type 4b, 4c and excluded patients with type 4a and type 5. For our study, we extracted data from CAMI database between January 1st, 2013 to September 30th, 2014 and identified a cohort of 26,082 patients. We excluded patients with missing or invalid data on in-hospital admission diagnosis (STEMI or NSTEMI), age, sex, BMI and finally, included 21,994 patients [Figure 1].

Data collection and definition

We extracted data on patient demographics, medical history, symptom on admission, time to hospital, diagnosis, and so on from CAMI database. Standardized questionnaire was used to collect data on symptomatology. Symptomatology assessment included persistent chest pain (≥ 20 min), dyspnea, nausea and vomiting, diaphoresis, syncope and incontinence. Atypical symptoms were defined as clinical presentation without chest pain. Chest distress is defined as a sensation of chest pressure or tightness. According to third universal definition of MI, patients who develop ST elevation in two contiguous leads were classified into STEMI group. In contrast, patients without ST elevation were classified into NSTEMI group.

Statistical analysis

We used mean \pm standard deviation (SD) or median (25th and 75th percentiles) to present continuous variables, and Counts (frequencies) to present categorical variables. Student *t* tests or rank tests were used to compare continuous variables, and Chi-square tests were used to compare categorical variables. A *P* value less than 0.05 was of statistical significance unless otherwise indicated. Multivariable logistic regression model was used to explore independent predictors of atypical symptoms. Candidate variables fitted in the model were based on previous reports and clinicians experience including: age, sex, diabetes, type of MI, anterior wall MI, Killip classification, heart rate, blood pressure, prodromal symptoms, body mass index (BMI), hypertension, smoking status, prior MI, prior percutaneous coronary intervention (PCI), prior coronary artery bypass graft (CABG), renal failure, prior angina, hyperlipidemia, history of family coronary artery disease (CAD), prior stroke and prior heart failure (HF). After stepwise selection, those variables with *P* < 0.05 were retained in the model. All analysis was performed with SAS 9.4 software (SAS Institute, USA).

Results

Baseline characteristics

Among 21,994 patients included in our study, a total of 16,315 (74.2%) patients had STEMI and the remaining 5679 (25.8%) patients had NSTEMI. Table 1 showed baseline characteristics between 2 groups. Compared with patients with STEMI, NSTEMI patients were older (mean age: 65.6 vs. 62.0 years, *P* < 0.0001) and more likely to be females (31.8% vs. 23.6%, *P* < 0.0001). NSTEMI patients were also more likely to have diabetes (24.7% vs. 18.7%, *P* < 0.0001), prior MI (11.9% vs. 5.9%, *P* < 0.0001), prior HF (5.9% vs. 1.5%, *P* < 0.0001), prior PCI (5.0% vs. 3.1%, *P* < 0.0001), prior CABG (0.9% vs. 0.3%, *P* < 0.0001), hypertension (59.5% vs. 48.7%, *P* < 0.0001), hyperlipidemia (8.4% vs. 6.8%, *P* < 0.0001) and non-smokers (51.9% vs. 43.1%, *P* < 0.0001).

Clinical symptoms by MI type

A total of 111 patients in NSTEMI group and 197 patients in STEMI group presented without symptoms (2% vs. 1.2%, *P* = 0.0001) [Table 2]. Most common symptoms in both NSTEMI and STEMI group were persistent precordial chest pain, diaphoresis, chest distress, and radiation pain. The proportion of persistent precordial chest pain (54.3% vs. 71.4%, *P* < 0.0001), diaphoresis (48.6% vs. 70.0%, *P* < 0.0001), radiation pain (26.4% vs. 33.8%, *P* < 0.0001), nausea or vomiting (19.1% vs. 30.1%, *P* < 0.0001), dysphoria (3.6% vs. 4.4%, *P* = 0.0079), syncope (2.3% vs. 2.9%, *P* = 0.0116) were lower among NSTEMI patients compared with STEMI patients. The proportion of chest distress (42.4% vs. 38.3%, *P* < 0.0001), shortness of breath (24.5% vs. 21.2%, *P* < 0.0001), palpitation (14.5% vs. 13.0%, *P* = 0.0055) and recurrent angina (5.9% vs. 2.6%, *P* < 0.0001) were higher in NSTEMI group compared with STEMI group.

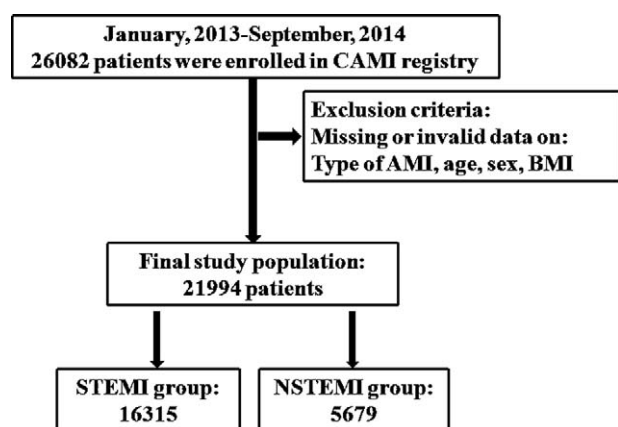


Figure 1: Study population. From January 2013 to September 2014, a total of 26,082 patients with AMI were registered, after excluding patients with missing or invalid data on admission diagnosis (STEMI or NSTEMI), BMI, age, gender, we finally included 21,994 patients (STEMI: 16,315, NSTEMI: 5679).

Table 1: Baseline characteristics of patients with STEMI vs. NSTEMI.

Variables	NSTEMI group (N=5679)	STEMI group (N=16315)	P value
Age (years)	65.58 ± 12.06	62.02 ± 12.47	<0.0001
Female	1806 (31.8)	3851 (23.6)	<0.0001
BMI (kg/m ²)	24.08 ± 3.24	24.15 ± 3.26	0.1643
Diabetes	1405 (24.7)	3045 (18.7)	<0.0001
Prior MI	673 (11.9)	969 (5.9)	<0.0001
Prior HF	333 (5.9)	24.4 (1.5)	<0.0001
Prior PCI	286 (5.0)	499 (3.1)	<0.0001
Prior CABG	52 (0.9)	41 (0.3)	<0.0001
Hypertension	3381 (59.5)	7939 (48.7)	<0.0001
Hyperlipidemia	479 (8.4)	1104 (6.8)	<0.0001
Smoking status			<0.0001
Never smoked	2950 (51.9)	7037 (43.1)	
Ex-smokers	745 (13.1)	1635 (10.0)	
Current-smokers	1984 (34.9)	7643 (46.8)	
Premature CAD	175 (3.1)	582 (3.6)	0.0802

Data were presented as mean ± SD or *n* (%) unless otherwise indicated. BMI: Body mass index; CABG: Coronary artery bypass graft; CAD: Coronary artery disease; HF: Heart failure; MI: Myocardial infarction; PCI: Percutaneous coronary intervention.

Table 2: Clinical symptoms of patients with STEMI vs. NSTEMI.

Symptoms	NSTEMI group (N=5679)	STEMI group (N=16315)	P value
Absence of symptoms	111 (2.0)	197 (1.2)	0.0001
Persistent precordial chest pain	3082 (54.3)	11650 (71.4)	<0.0001
Diaphoresis	2761 (48.6)	11416 (70.0)	<0.0001
Chest distress	2410 (42.4)	6244 (38.3)	<0.0001
Radiation pain	1500 (26.4)	5516 (33.8)	<0.0001
Nausea/Vomiting	1084 (19.1)	4916 (30.1)	<0.0001
Shortness of breath	1389 (24.5)	3466 (21.2)	<0.0001
Fatigue	1009 (17.8)	2934 (18.0)	0.7142
Palpitation	822 (14.5)	2122 (13.0)	0.0055
Dysphoria	205 (3.6)	721 (4.4)	0.0079
Recurrent angina pectoris	334 (5.9)	417 (2.6)	<0.0001
Back pain	147 (2.6)	447 (2.7)	0.5428
Syncope	129 (2.3)	472 (2.9)	0.0116
Persistent upper abdomen pain	132 (2.3)	385 (2.4)	0.8792
Mandibular /Tooth pain	66 (1.2)	193 (1.2)	0.9003
Incontinence	22 (0.4)	77 (0.5)	0.4047

Data were presented as *n* (%).

Time to hospital by MI type

Table 3 showed time to hospital among patients with NSTEMI vs. STEMI. More patients in NSTEMI group presented to hospital 1 to 7 days (41.5% vs. 23.8%) or 12 to 24 h (13.9% vs. 10.3%) after presentation, fewer patients in NSTEMI group presented to hospital less than 3 h (14.5% vs. 23.5%), *P* value less than 0.0001.

Independent predictors of atypical symptoms

Multivariable logistic model was used to explore independent predictors of atypical symptoms. After stepwise selection, the following variables were identified as

independent predictors of atypical symptom and were shown in Table 4: age, DM, NSTEMI, higher Killip classification level, heart rate, systolic blood pressure and the presence of prodromal symptoms. Of note, after adjustment for confounders including age, sex, diabetes, type of MI, anterior wall MI, Killip classification, heart rate, blood pressure, prodromal symptoms, BMI, hypertension, smoking status, PCI, prior CABG, renal failure, prior angina, hyperlipidemia, family history of CAD, prior stroke, prior HF, type of MI (NSTEMI vs. STEMI) was still associated with atypical symptoms. NSTEMI independently predicted presentation of atypical symptom (odds ratio (OR): 1.974, 95% confidence interval (CI): 1.849-2.107).

Discussion

In the analysis of a large-scale prospective registry, we found that compared with patients with STEMI, fewer patients with NSTEMI presented with persistent chest pain, diaphoresis and radiation chest pain and more patients presented with chest distress. Time from symptom onset to hospital was longer among NSTEMI patients.

In multivariable analysis, NSTEMI was an independent predictor of atypical symptom.

There were several large-scale previous studies describing and comparing clinical characteristics of AMI patients with *vs.* without typical chest pain. These studies used data from different registries including Korea Acute Myocardial Infarction Registry (KAMIR) registry,^[2] The Global Registry of Acute Coronary Events (GRACE) registry,^[3] National registry of myocardial infarction (NRMII)^[4,10] and Japanese registry of acute Myocardial INfarction diagnosed by Universal dEfiniTion (J-MINUET).^[5] These studies showed that painless STEMI had higher in-hospital mortality than painful STEMI,^[2,3] presentation without chest pain were more common among NSTEMI patients and proportion of ST-segment elevation was less common among patients without chest pain.^[4,5] Another large-scale registry-based study enrolled 1,143,513 patients with MI from 1977 hospitals and found patients with chest pain were more likely to present STEMI and those without chest pain were more likely to present NSTEMI. Although this study didn't directly compare symptoms between STEMI and NSTEMI patients, it indicated that NSTEMI patients

were more likely to present without typical chest pain.^[11] However, these studies had several major limitations: symptoms were not compared between STEMI and NSTEMI patients, and details of presenting complaints among those without chest pain (ie, dyspnea, nausea, and so on) were not provided. Our study is the first large-scale study describing and comparing symptoms of NSTEMI *vs.* STEMI in details and is useful to enhance clinicians' awareness of wide spectrum of symptoms among NSTEMI patients.

There are differences in AMI characteristics between China and other countries. In Europe and USA, NSTEMI are more common than STEMI while in China STEMI is still the dominant type of AMI.^[12] However, the proportion of NSTEMI is increasing, highlighting the importance to learn more about NSTEMI symptoms. Second, prehospital delay time is longer in China compared with other countries: decision time (from symptom onset to decision to seek medical help) in China was 130 min, which was longer than that in other countries (UK: 121 min; Canada: 98 min; Sweden: 110 min).^[13] Of note, seeking non-emergent medical care was the most popular action when no chest pain occurs.^[14] In summary, these data as well as our results highlighted that improvement in the management of AMI is still needed. First, patients should be educated more about possible symptoms of AMI, particular atypical symptoms in order to reduce prehospital patient delay and receive medical care as soon as possible. In addition, clinicians should increase the awareness of NSTEMI, particularly for those with atypical symptoms including chest distress and non-ST elevation on ECG.

Several factors may be associated with atypical symptoms among NSTEMI patients: It is generally thought that patients with NSTEMI had smaller infarct size than STEMI patients, and the infarct does not involve full thickness of the myocardium or epicardium. A magnetic resonance-based study also indicated that NSTEMI patients had smaller infarct size and area at risk, as well as less reperfusion injury than STEMI patients.^[10] When a heart attack occurs, the sensation of pain started with activation of afferent nerve, which predominantly locates

Table 3: Time to hospital of patients with NSTEMI vs. STEMI, n (%).

Time to hospital	NSTEMI group (N=5679)	STEMI group (N=16315)	P value
> 1-7 days	2357 (41.5)	3878 (23.8)	<0.0001
> 12-24 h	788 (13.9)	1675 (10.3)	
> 6-12 h	924 (16.3)	4299 (26.3)	
3-6 h	787 (13.9)	2630 (16.1)	
<3 h	823 (14.5)	3833 (23.5)	

Table 4: Independent predictors of atypical symptoms.

Variables	Odds ratio	95% Confidence interval	
Age (per 1 year increase)	1.016	1.013	1.019
Diabetes mellitus	1.112	1.034	1.196
NSTEMI <i>vs.</i> STEMI	1.974	1.849	2.107
Killip classification			
II <i>vs.</i> I	1.143	1.057	1.237
III <i>vs.</i> I	1.803	1.585	2.051
IV <i>vs.</i> I	1.691	1.462	1.954
Heart rate (per 1 beats/min increase)	1.006	1.004	1.007
Systolic blood pressure (per 1 mmHg increase)	0.998	0.997	1.000
Current smoker <i>vs.</i> nonsmoker	0.847	0.788	0.910
Presence of prodromal symptoms	0.790	0.741	0.843

Adjusted for age, sex, diabetes, type of MI, anterior wall MI, Killip classification, heart rate, blood pressure, prodromal symptoms, BMI, hypertension, smoking status, PCI, prior CABG, renal failure, prior angina, hyperlipidemia, family history of CAD, prior stroke, prior HF.

in outer epicardium.^[15] As discussed above, NSTEMI patients may involve less epicardium and afferent nerve activation, and therefore perceive less pain but more atypical symptoms.^[3]

Another major finding of our study is that NSTEMI patients had longer time from symptom onset to hospital, which was also demonstrated in several other large-scale studies. Data from GRACE registry indicated that NSTEMI patients had longer pre-hospital patient delay than STEMI patients (3.1 h *vs.* 2.5 h, $P < 0.05$), irrespective of geographic region.^[16] Miyachi *et al* used data from Tokyo CCU network database and found that NSTEMI patients had higher onset-to-door time (233 *vs.* 165 min, $P < 0.001$) and higher door to balloon time (145 *vs.* 60 min, $P < 0.001$) than STEMI patients.^[17] In addition, PCI-related delay was also longer among NSTEMI patients (32.9 *vs.* 3.5 min, $P < 0.001$).^[18]

Possible explanations for longer patient delay include: Compared with patients with STEMI, more patients with NSTEMI had prior angina pectoris^[19] and were accustomed to ischemic symptoms. Therefore, they were less likely to identify symptoms associated with new-onset AMI. In addition, consistent with our results, many previous studies demonstrated that patients with NSTEMI tend to be older and have more comorbidities including heart failure, stroke, and diabetes.^[18,20-22] Identification of cardiac origin symptoms may be masked by these chronic diseases and therefore leading to pre-hospital delay. Our results confirmed that prompt recognition of AMI symptoms and signs were of clinical significance for reducing pre-hospital patient delay and improving outcome for NSTEMI patients in particular.

Our study had large sample size and detailed description of symptoms particular for those patients without chest pain. Diagnostic criteria were clear and well accepted. However, there are several limitations of our study: all participants were from China, it remains unclear whether there is ethnic difference in symptoms of AMI. Our study did not account for follow-up data. Whether NSTEMI has impact on short or long-term prognosis needs further investigation. Finally, our study was an observational non-randomized registry based study which may subject to selection bias related to this type of clinical investigation.

Compared with patients with STEMI, those with NSTEMI were less likely to present with typical chest pain, diaphoresis and radiation chest pain and more likely to have chest distress. Patients with NSTEMI also had longer time to hospital than patients with STEMI. Our results were useful for both clinicians and patients to gain deeper understanding of symptoms of NSTEMI and reduce pre-hospital patient delay.

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Data sharing statement

Data are available from the corresponding author on reasonable request.

Conflicts of interest

None.

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